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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/723,610	11/26/2003	Ning Hu	01992.006US1	7912

53137 7590 03/28/2007
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EXAMINER	
KISHORE, GOLLAMUDI S	
ART UNIT	PAPER NUMBER
1615	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/28/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/723,610	HU ET AL.	
	Examiner	Art Unit	
	Gollamudi S. Kishore, Ph.D	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-71 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-71 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date 11-12-07.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claim Rejections - 35 USC § 112

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 1-71 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

(a) in claim 1 and 63 is confusing. The pharmaceutical agent is added in an acidic solution which is proton rich; if the agent is a weak base, then it is in a protonated form in an acidic solution and no unprotonated agent exists. If so, what is meant by 'wherein the unprotonated form of the pharmaceutical agent is uncharged and is capable of permeating the membrane of the liposome? If the active agent is either anionic or cationic then in an unprotonated state they will be charged and in a protonated state they will be neutral. In either case, this limitation does not make sense. Furthermore, if the pH of the liposome interior is not recited, it does not make sense to recite only the acidic nature of the added medium to the liposomes.

Claim 43 recites 'the method of claim 1 wherein the solution---'. A) in claim 1 recites two solutions. Which solution of claim 1 applicant is referring to in claim 43? Furthermore, according to claim 1, the solution of a) which is cooled is contacted with a weak base; however, according to claim 43, the external solution is removed by filtration meaning that the liposomes prepared do not have an external phase. This is contradictory to claim 1 limitation.

Claim Rejections - 35 USC § 102

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4. Claims 1-6, 8-26, 28-29, 32, 40-51 and 58-71 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 99/13816 of record.

WO 99 discloses a method of loading camptothecins using a pH gradient at a higher temperature, which is same as instant method. The lipids used include DSPC, cholesterol and phosphatidyl glycerols. The buffer used is citrate buffer which is more than 5 mM, preferably 50 mM. The lipid to camptothecin ratios are from 5:1 to 100:1. The method of treatment includes treatment of head and neck cancers (abstract, pages 10-15, 18, Example 2 and claims). Since it is the same composition, the reduction of toxicity and lower incidence in side effects are inherent.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 1-44, 47-48, 51 and 58-71 are rejected under 35 U.S.C. 103(a) as being unpatentable over EP 0 719 546 or WO 99/13816 both are of record by themselves or in combination.

EP discloses a method of loading active agents using a pH gradient at a higher temperature. The method is applicable to several anti-cancer agents such as doxorubicin, vincristine, purine or pyrimidine compounds, antibiotics and others. The lipids used are EPC and cholesterol. Other phospholipids suggested are DSPC, DPPC, DMPC and DAPC. Although in examples, EP teaches the loading of doxorubicin at a higher pH than the interior pH of the liposomes, on col. 20, lines 44-49 it teaches that pH gradients can be established with a second external medium of relatively acidic or basic pH. Therefore, it would have been obvious to one of ordinary skill in the art to load an active agent at an acidic medium and then relative to the liposome interior and then change the pH of the exterior to basic pH such that the active agent remains entrapped. Although EP does not disclose the use of phosphatidylglycerol in the liposomes, since it is the commonly used negatively charged lipid to provide negative charge to the liposomes, it would have been obvious to one of ordinary skill in the art to include this phospholipid with a reasonable expectation of success. One of ordinary skill in the art would be motivated further to include this lipid since WO which is discussed below advocates the use of this lipid in similar active agent loading method.

WO 99 discloses a method of loading camptothecins using a pH gradient at a higher temperature, which is same as instant method. The lipids used include DSPC, cholesterol and phosphatidyl glycerols. The buffer used is citrate buffer which is more than 5 mM. The lipid to camptothecin ratios are from 5:1 to 100:1 (abstract, pages 10-15, 18, Example 2 and claims). Although in examples, WO uses citric acid at 50 mM concentration, in view of WO's teachings that it can be higher than 5 mM, it would have

been obvious to one of ordinary skill in the art to vary the molarity up to 60 mM with the expectation of obtaining the best possible results. Although WO does not teach the loading of active agents other than camptothecins, it would have been obvious to one of ordinary skill in the art to load any agent since the principle of loading is the same. One of ordinary skill in the art would be motivated to load any active agent since EP, which uses similar loading procedure, teaches that several active agents could be loading using the pH gradient method. Although neither EP nor WO teach the use of sphingomyelin in the preparation of the liposomes, since it is a commonly used lipid in the liposome formations, it would have been obvious to one of ordinary skill in the art to use this lipid with a reasonable expectation of success. Although EP and WO do not teach all of the claimed ratios of the components, it would have been obvious to one of ordinary skill in the art to vary the amounts of the components with the expectation of obtaining the best possible results.

7. Claims 7, 45-46 and 49 rejected under 35 U.S.C. 103(a) as being unpatentable over EP 0 719 546 or WO 99/13816 both are of record by themselves or in combination as set forth above, further in view of Webb (5,814,335) of record.

The teachings of EP and WO have been discussed above. What is lacking in these references is the use of sphingomyelin as the liposome-forming lipid. The use of sphingomyelin however, would have been obvious to one of ordinary skill in the art since Webb teaches that sphingomyelin containing liposomes are stable and have extended circulation time (abstract). Neither EP nor WO teaches the change of the pH of the external medium by using methylamine. The use of methylamine to change the

pH of the external medium would have been obvious to one of ordinary skill in the art with a reasonable expectation of success since Webb teaches the creation of pH gradient using methylamine (columns 7 and 8).

8. Claims 52-57 are rejected under 35 U.S.C. 103(a) as being unpatentable over EP 0 719 546 or WO 99/13816 both are of record by themselves or in combination as set forth above, further in view of Clerc (5,939,096).

The teachings of EP and WO have been discussed above. What is lacking in these references is the teaching of dehydrating the liposomes in the presence of cryoprotectants.

Clerc while disclosing a method of drug loading by pH gradient teaches that liposomes can be dehydrated for storage in the presence of cryoprotectant sugars (col. 8, lines 9-15). It would have been obvious to one of ordinary skill in the art to use cryoprotectants and dehydrate liposomes since they can be stored in that state as taught by Clerc.

Double Patenting

9. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

10. Claims 1-71 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-71 of copending Application No. 10/723,431. Although the conflicting claims are not identical, they are not patentably distinct from each other because claims in both applications are drawn to the same method of loading active agents into liposomes. In instant claims, the acid used has 'up to 60 mM concentration whereas the acid recited in the copending application has 'at least about 60 mM concentration'. First of all the upper limit in instant claims and the lower limit in the claims of copending application overlap since 'about' provides some flexibility. Furthermore, since the active agent is loaded using a pH gradient, it would have been obvious to one of ordinary skill in the art to vary the amounts of the acid to obtain the best possible results.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

11. Claims 1-71 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 30-31 and 35-64 of U.S. Patent No. 6,740,335 by itself or in combination with EP cited above. Although the conflicting claims are not identical, they are not patentably distinct from each other because both

patented claims and instant claims are drawn to the process of loading agents using pH gradients. Instant claims are generic with respect to the active agents loaded whereas the patented claims recite specific camptothecin compound. However, it would have been obvious to one of ordinary skill in the art to load any active agent using a pH gradient with a reasonable expectation of success. One of ordinary skill in the art would be motivated further to use the method to load any compound since the reference of EP shows that any compound can be loaded using pH gradient as discussed above. Patented claims do not recite the concentration of the acid while loading the active agent and instant mM amounts therefore, are deemed to be anticipated by the claims in the patent.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gollamudi S. Kishore, Ph.D whose telephone number is (571) 272-0598. The examiner can normally be reached on 6:30 AM- 4 PM, alternate Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Woodward Michael can be reached on (571) 272-8373. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Gollamudi S Kishore, Ph.D
Primary Examiner
Art Unit 1615

GSK